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EXAMINER	
BLANCHARD, DAVID J	

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1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/623,039	BANERJEE ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *5,7-11,13,16,17,19,21,24 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,12,14,15,18,20,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*. See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/6/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-23, drawn to a method of treating a subject suffering from spondyloarthropathy comprising administering a human antibody that binds TNF-α, classified in class 424, subclass 145.1.

   II. Claims 24-25, drawn to a kit comprising a human TNF-α antibody, classified in class 530, subclass 388.23.

2. This application contains claims directed to the following patentably distinct species, i.e., the TNFα-related disorders (e.g., see claims 5, 6, 13, 14, 19 and 20). The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1-4, 12, 15, 18 and 22-23 are generic.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

3. The inventions are distinct, each from the other because of the following reasons:

Inventions II and I are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the antibody of Group II can be used to purify the antigen in addition to the materially different therapeutic method of Group I, which differs in the method objective, method steps, parameters, reagents used and endpoints.

4. Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above

and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;
(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;
(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);
(d) the prior art applicable to one invention would not likely be applicable to another invention;
(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention.**

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

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Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable

over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

5. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. Process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. Failure to do so may result in a loss of the right to rejoinder.

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(l).

7. During a telephone conversation with Tara Seshadri on 06 September 2007 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-23 and the species "psoriatic arthritis". Affirmation of this election must be made by applicant in replying to this Office action. Claims 5, 7-11, 13, 16-17, 19, 21 and 24-25 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

8. Claims 1-4, 6, 12, 14-15, 18, 20 and 22-23 are under consideration to the extent that the spoondyloarthropathy is psoriatic arthritis, i.e., applicants' elected species.

Information Disclosure Statement

9. The information disclosure statement (IDS) submitted on 06 April 2004 has been fully considered by the examiner. A signed copy of the IDS submitted on 06 April 2004 is included with the instant Office Action.

Specification

10. The disclosure is objected to because of the following informalities:

a. The specification discloses various non-provisional US Application numbers that should be updated with their current status, i.e., "now abandoned" or "U.S. Patent Number ....", or updated during the pendency of the present application should their status change. For example, see pg. 1, lines 13-29, pg. 7, line 27, pg. 8, line 12 and pg. 9, line 9. Applicants' cooperation is requested in reviewing the entire disclosure for additional non-provisional U.S. Application Numbers that require updating.

b. The specification at pg. 1 references several US Application numbers according to "Attorney Docket No. ", which should be corrected with the appropriate US Application Serial numbers or US Patent numbers and current status indicated for the application numbers.

c. The use of various trademarks have been noted in this application. For example, see pp. 3, 5, 7-8, 16, 29, 31 as well as others. It should be capitalized wherever it appears and be accompanied by the generic terminology. Applicants' cooperation is requested in reviewing the entire disclosure for additional trademarks that require correction.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

d. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the treatment of a psoriatic arthritis using human TNFα antibodies.

Appropriate correction is required.

Claim Objections

11. Claim 15 is objected to as depending from withdrawn claim 13.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

13. Claims 4, 15, 18, 20 and 22-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 4, 15, 18, 20 and 22-23 are vague and indefinite in the recitation of "D2E7" as the sole means of identifying the antibody referred to in the claims. The use of laboratory designations to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. This rejection can be overcome by amending the claims to specifically and uniquely identify "D2E7", for example, by SEQ ID number of the complete antibody (i.e., complete heavy and light chain sequences) or by biological deposit.

b. Claims 4 and 15 are indefinite in the recitation "antigen-binding fragment thereof, is D2E7". The specification discloses that D2E7 is also known as HUMIRA®, which is a human anti-TNF-alpha monoclonal antibody (see pp. 15 and 18). Thus, given that an antibody and an antigen-binding fragment thereof are different molecules and while an antigen-binding fragment can be produced from antibody D2E7, one of skill in the art would not be reasonably apprised of the metes and bounds of D2E7 being an antibody and an antigen-binding fragment thereof. Is the antigen-binding fragment an antigen-binding fragment of D2E7?

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 4, 15, 18, 20 and 22-23 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological

materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line, which produces an antibody having the exact chemical identity of antibody D2E7 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. Fundamental Immunology, William E. Paul, M.D. ed., 3rd ed., pg. 242, 1993. Therefore, it would require undue experimentation to reproduce the claimed antibody species antibody D2E7.

The specification lacks complete deposit information for the deposit of anti-TNFα antibody D2E7. It is unclear whether antibodies possessing the identical properties of antibody D2E7 are known and publicly available or can be reproducibly isolated from nature without undue experimentation.

Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed antibody D2E7, a suitable deposit is required for patent purposes, evidence of public availability of the claimed antibody or evidence of the reproducibility without undue experimentation of the claimed antibody, is required.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit of antibody D2E7 has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit of antibody D2E7 is not made under the provisions of the Budapest Treaty, then in order to certify that the deposit complies with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

> (a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:
> (b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:
> (c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and
> (d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed. See MPEP 2406 and 37 CFR 1.804(b).

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

16. Claims 2 and 6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating psoriatic arthritis in a subject comprising administering a human anti-human TNFα antibody or antigen-binding fragment thereof comprising a light chain comprising CDR1 of SEQ ID NO:7, CDR2 of SEQ ID NO:5 and CDR3 of SEQ ID NO:3, optionally comprising the recited amino acid substitutions and a heavy chain comprising CDR1 of SEQ ID NO:8, CDR2 of SEQ ID NO:6 and CDR3 of SEQ ID NO:4, optionally comprising the recited amino acid substitutions, does not reasonably provide enablement for a method of treating psoriatic arthritis in a subject comprising administering a human anti-human TNFα antibody or antigen-binding fragment thereof comprising a light chain comprising CDR3 of SEQ ID NO:3, optionally comprising the recited amino acid substitutions and a heavy chain comprising a heavy chain comprising CDR3 of SEQ ID NO:4, optionally comprising the recited amino acid substitutions as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention is engineered antibodies and immunotherapy where the relative level of skill of those in the art is deemed to be high.

The claims are broadly drawn to a method of treating a subject suffering from psoriatic arthritis comprising administering a human anti-human TNFα antibody or antigen-binding fragment thereof that dissociates from human TNFα with a K_{off} of 1 x 10^{-3} s^{-1} or less, as determined by surface plasmon resonance; (b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:3, or modified from SEQ ID NO:3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9; (c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12. Thus, the claims encompass anti-human TNFα antibodies that comprise the CDR3 regions, or mutant CDR3 regions of antibody D2E7 and do not comprise the heavy and light chain CDR1 and CDR2 regions from antibody D2E7 for the clinical treatment of psoriatic arthritis.

The specification discloses only human anti-human TNFα antibodies and antigen-binding fragments thereof that comprise all six CDRs, three from the heavy chain and three from the light chain of human anti-human TNFα antibody D2E7 (see examples). The specification does not teach human anti-human TNFα antibodies or antigen-binding fragments thereof that only comprise the mutant CDR3 regions of the heavy and light chains of antibody D2E7, which do not contain the CDR1 and CDR2 regions of antibody D2E7 and do not bind human TNFα. There are no working examples of human anti-human TNFα antibodies or antigen-binding fragments thereof

that only comprise the mutant CDR3 regions of the heavy and light chains of antibody D2E7, wherein the antibodies or antigen-binding fragments thereof bind human TNFα and dissociates from human TNFα with a K_{off} of 1×10^{-3} s^{-1} or less. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

The state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of antibodies routinely requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, 3rd Edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79(6):1979-1983, March 1982). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. While there are some publications, which acknowledge that CDR3 is important, the conformations of other CDRs as well as framework residues influence binding. MacCallum et al (J. Mol. Biol., 262, 732-745, 1996) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR

definitions make antigen contacts (see page 733, right col.) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.). The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset et al (Biochemical and Biophysical Research Communications, 307:198-205, 2003), which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset et al also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left col.). It is unlikely that human anti-human TNFα antibodies and antigen-binding fragments thereof, which do not contain all of the heavy and light chain CDRs of antibody D2E7 in their proper order and in the context of framework sequences which maintain their correct spatial orientation have the requisite human TNFα -binding function. There is insufficient guidance and direction to assist those skilled in the art in producing human anti-human TNFα antibodies that only comprise mutant CDR3 regions of antibody D2E7 that bind human TNFα. Applicants have provided insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing human anti-human TNFα antibodies, which contain less than the full complement of CDRs from antibody D2E7 and comprising the recited heavy and light chain CDR3 amino acid substitutions, wherein the antibody binds human TNFα and dissociates from human TNFα with a K_{off} of 1×10^{-3} s^{-1} or less and effectively treats psoriasis associated with rheumatoid arthritis in a subject. One of skill in the art would neither expect nor predict the appropriate functioning of the human anti-human TNFα antibodies as broadly as is claimed.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Paul W. E., Rudikoff et al, MacCallum et al and Casset et al the lack of guidance and direction provided by applicant, and the absence of working examples,

undue experimentation would be required to practice the claimed therapeutic method comprising human anti-human TNFα antibodies, which contain less than the full complement of CDRs of antibody D2E7 with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed human anti-human TNFα antibodies and absent working examples providing evidence which is reasonably predictive that the claimed human anti-human TNFα antibodies bind human TNFα and dissociates from human TNFα with a K_{off} of 1×10^{-3} s^{-1} or less, commensurate in scope with the claimed invention.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 1-4, 6, 12, 14-15, 18, 20 and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ogilvie et al (British Journal of Dermatology, 144(3):587-589, March 2001) in view of Salfeld et al [a] (WO 97/29131, publication date 8/14/1997, IDS reference A4 filed 4/6/04) and Smith et al (Arthritis Rheum. 23(8):961-962, August 1980).

The claims are being interpreted as drawn to a method of treating a subject suffering from psoriatic arthritis comprising administering a therapeutically effective amount of a neutralizing, high affinity TNFα antibody or antigen-binding fragment thereof such that psoriatic arthritis is treated, wherein the antibody is an isolated human antibody or antigen-binding fragment thereof that dissociates from human TNFα with a K_d of 1×10^{-8} M or less and a K_{off} of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1×10^{-7} M or less, and wherein the isolated human antibody or antigen-binding fragment thereof antibody has the following characteristics: (a) dissociates from human TNFα with a K_{off} of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance; (b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:3, or modified from SEQ ID NO:3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9; (c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12, and wherein the isolated human antibody or antigen-binding fragment thereof comprises a light chain variable region comprising SEQ ID NO:1 and a heavy chain variable region comprising SEQ ID NO:2 and the antibody is D2E7, or is administered with one additional therapeutic agent selected from the group consisting of ibuprofen, diclofenac and misoprostol, naproxen, meloxicam, indomethacin and diclofenac.

Ogilvie et al teach a method of treating psoriatic arthritis in patients comprising administering the chimeric anti-TNFα monoclonal antibody, Infliximab, which resulted in a dramatic improvement in arthritis and showed rapid improvement of their psoriatic arthritis (see entire document, particularly Fig. 1). Ogilvie et al do not specifically teach the presently claimed human antibody or antigen-binding fragment thereof that dissociates from human TNFα with a K_d of 1×10^{-8} M or less and a K_{off} of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1×10^{-7} M or less, and wherein the isolated human antibody or antigen-binding fragment thereof antibody has the following characteristics: (a) dissociates from human TNFα with a K_{off} of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance; (b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:3, or modified from SEQ ID NO:3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9; (c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12, and wherein the isolated human antibody or antigen-binding fragment thereof comprises a light chain variable region comprising SEQ ID NO:1 and a heavy chain variable region comprising SEQ ID NO:2 and the antibody is D2E7, or is administered with one additional therapeutic agent selected from the group consisting of ibuprofen, diclofenac and misoprostol, naproxen, meloxicam, indomethacin and diclofenac. These deficiencies are made up for in the teachings of Salfeld et al [a] and Smith et al.

Salfeld et al [a] teach that because chimeric and humanized antibodies still retain some of murine sequence, they still may elicit an unwanted immune reaction in human patients and Salfeld et al [a] teach a method for treating TNFα-related disorders in a subject comprising administering a therapeutically effective amount of a neutralizing, high affinity human anti-human TNFα antibody or antigen-binding fragment thereof

identical to the claimed human anti-human TNFα antibodies, i.e., dissociates from human TNFα with a K_d of 1 x 10^{-8} M or less and has a K_{off} of 1 x 10^{-3} s^{-1} or less, as determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1 x 10^{-7} M or less, and the human antibody or antigen-binding fragment thereof antibody has the following characteristics: (a) dissociates from human TNFα with a K_{off} of 1 x 10^{-3} s^{-1} or less, as determined by surface plasmon resonance; (b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:3, or modified from SEQ ID NO:3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9; (c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12, and wherein the human antibody or antigen-binding fragment thereof comprises a light chain variable region comprising SEQ ID NO:1 and a heavy chain variable region comprising SEQ ID NO:2 and the antibody is D2E7 and is administered with one or more additional therapeutic agents (see entire document, particularly pp. 2-4, 5-6, 12-15, 29-31 and 35-40).

Smith et al teach that administration of ibuprofen in patients suffering from psoriatic arthritis effectively decreases pain and joint swelling (see entire document).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the neutralizing, high affinity human anti-human TNFα antibodies or an antigen-binding fragment thereof of Salfeld et al [a], and administered with ibuprofen for therapeutic benefit in psoriatic arthritis patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to use the neutralizing, high affinity human anti-human TNFα antibodies or an antigen-binding fragment thereof of Salfeld et al [a], and administered with ibuprofen for therapeutic benefit in psoriatic arthritis patients in view of Ogilvie et al and Smith et al because

Ogilvie et al teach a method of treating psoriatic arthritis in patients comprising administering the chimeric anti-TNFα monoclonal antibody, Infliximab, which resulted in a dramatic improvement in arthritis and showed rapid improvement of their psoriatic arthritis, however, Salfeld et al [a] teach that because chimeric and humanized antibodies still retain some of murine sequence, they still may elicit an unwanted immune reaction in human patients and Salfeld et al [a] teach neutralizing, high affinity human anti-human TNFα antibody and antigen-binding fragments thereof for treating TNFα-related disorders in a subject comprising administering a therapeutically effective amount of a human anti-human TNFα antibody or antigen-binding fragment thereof identical to the claimed human anti-human TNFα antibodies, i.e., identical structures/sequences, binding kinetics and neutralization properties (discussed supra) and administered with one or more additional therapeutic agents and Smith et al teach that administration of ibuprofen in psoriatic arthritis patients effectively decreases pain and joint swelling. Therefore, one of ordinary skill in the art would have been motivated to modify the method of Ogilvie et al and administer the human anti-human TNFα antibodies and antigen-binding fragments thereof of Salfeld et al [a] in combination with ibuprofen in order to avoid any unwanted immune reaction in human patients due to the presence of murine sequences in the chimeric anti-TNFα antibody of Ogilvie et al and reduce pain and joint swelling in psoriatic arthritis patients. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). See also, *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007). Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to produce a method of treating psoriatic arthritis in a human patient comprising administering the neutralizing, high affinity human anti-human TNFα antibodies or an antigen-binding fragment thereof of Salfeld et al [a], and

administered with at ibuprofen in view of the teachings of Ogilvie et al and Salfeld et al [a] and Smith et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

19. Claims 1-4, 6, 12, 14-15, 18, 20 and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ogilvie et al (British Journal of Dermatology, 144(3):587-589, March 2001) in view of Salfeld et al [b] (U.S. Patent 6,509,015 B1, 2/9/1996, IDS reference A2 filed 4/6/04) and Smith et al (Arthritis Rheum. 23(8):961-962, August 1980).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The claims and their interpretation have been described supra.

Ogilvie et al have been described supra. Ogilvie et al do not specifically teach the presently claimed human antibody or antigen-binding fragment thereof that dissociates from human TNFα with a K_d of 1×10^{-8} M or less and a K_{off} of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1×10^{-7} M or less, and wherein the isolated human antibody or antigen-binding fragment thereof antibody has the following characteristics: (a) dissociates from human TNFα with a K_{off} of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance; (b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:3, or modified from SEQ ID NO:3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9; (c) has a

heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12, and wherein the isolated human antibody or antigen-binding fragment thereof comprises a light chain variable region comprising SEQ ID NO:1 and a heavy chain variable region comprising SEQ ID NO:2 and the antibody is D2E7, or is administered with one additional therapeutic agent selected from the group consisting of ibuprofen, diclofenac and misoprostol, naproxen, meloxicam, indomethacin and diclofenac. These deficiencies are made up for in the teachings of Salfeld et al [b] and Smith et al.

Salfeld et al [b] teach that because chimeric and humanized antibodies still retain some of murine sequence, they still may elicit an unwanted immune reaction in human patients and Salfeld et al [b] teach neutralizing, high affinity human anti-human TNFα antibody and antigen-binding fragments thereof for treating TNFα-related disorders in a subject comprising administering a therapeutically effective amount of a human anti-human TNFα antibody or antigen-binding fragment thereof identical to the claimed human anti-human TNFα antibodies, i.e., dissociates from human TNFα with a K_d of 1 x 10^{-8} M or less and has a K_{off} of 1 x 10^{-3} s^{-1} or less, as determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1 x 10^{-7} M or less, and the human antibody or antigen-binding fragment thereof antibody has the following characteristics: (a) dissociates from human TNFα with a K_{off} of 1 x 10^{-3} s^{-1} or less, as determined by surface plasmon resonance; (b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:3, or modified from SEQ ID NO:3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9; (c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12, and wherein the human antibody or antigen-binding

fragment thereof comprises a light chain variable region comprising SEQ ID NO:1 and a heavy chain variable region comprising SEQ ID NO:2 and the antibody is D2E7 and is administered with one or more additional therapeutic agents (see entire document, particularly columns 2-4, 9-13, 22 and 25).

Smith et al have been described supra.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the neutralizing, high affinity human anti-human TNFα antibodies or an antigen-binding fragment thereof of Salfeld et al [b], and administered with ibuprofen for therapeutic benefit in psoriatic arthritis patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to use the neutralizing, high affinity human anti-human TNFα antibodies or an antigen-binding fragment thereof of Salfeld et al [b], and administered with ibuprofen for therapeutic benefit in psoriatic arthritis patients in view of Ogilvie et al and Smith et al because Ogilvie et al teach a method of treating psoriatic arthritis in patients comprising administering the chimeric anti-TNFα monoclonal antibody, Infliximab, which resulted in a dramatic improvement in arthritis and showed rapid improvement of their psoriatic arthritis, however, Salfeld et al [b] teach that because chimeric and humanized antibodies still retain some of murine sequence, they still may elicit an unwanted immune reaction in human patients and Salfeld et al [b] teach neutralizing, high affinity human anti-human TNFα antibody and antigen-binding fragments thereof for treating TNFα-related disorders in a subject comprising administering a therapeutically effective amount of a human anti-human TNFα antibody or antigen-binding fragment thereof identical to the claimed human anti-human TNFα antibodies, i.e., identical structures/sequences, binding kinetics and neutralization properties (discussed supra) and administered with one or more additional therapeutic agents and Smith et al teach that administration of ibuprofen in psoriatic arthritis patients effectively decreases pain and joint swelling. Therefore, one of ordinary skill in the art would have been motivated to modify the method of Ogilvie et al et al using the human anti-human TNFα antibodies

or an antigen-binding fragment thereof of Salfeld et al [b] in combination with ibuprofen in order to avoid any unwanted immune reaction in human patients due to the presence of murine sequences in the chimeric anti-TNFα antibody of Ogilvie et al and reduce pain and joint swelling in psoriatic arthritis patients. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). See also, *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007). Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to produce a method of treating a human patient suffering from psoriatic arthritis comprising administering the neutralizing, high affinity human anti-human TNFα antibodies or an antigen-binding fragment thereof of Salfeld et al [b], administered with ibuprofen in view of the teachings of Ogilvie et al and Salfeld et al [b] and Smith et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 1-4, 6, 12, 14-15, 18, 20 and 22-23 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 36-39 and 69 of U.S. Patent No. 6,509,015 B1 in view of Ogilvie et al (British Journal of Dermatology, 144(3):587-589, March 2001) and Smith et al (Arthritis Rheum. 23(8):961-962, August 1980). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims have been described supra.

Claims 1-7, 36-39 and 69 of U.S. Patent No. 6,509,015 B1 are drawn to a method of inhibiting human TNFα activity in a human subject suffering from rheumatoid arthritis and treating a human subject suffering from a disorder in which TNFα activity is detrimental comprising administering to the human subject a human anti-human TNFα antibody or antigen-binding fragment thereof that is identical to the neutralizing, high affinity human anti-human TNFα antibodies and antigen-binding fragments thereof of the present claims, i.e., identical structures/sequences, binding kinetics and neutralization properties and wherein the human anti-human TNFα antibody or antigen-binding fragment thereof is administered with at least one additional therapeutic agent.

Ogilvie et al have been described supra.

Smith et al have been described supra.

The claims in the instant application are obvious variants of claims 1-7, 36-39 and 69 of U.S. Patent No. 6,509,015 B1 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the method of claims 1-7, 36-39 and 69 of U.S. Patent No. 6,509,015 B1 comprising administering the human anti-human TNFα antibodies for the treatment of psoriatic arthritis and optionally

administer the human anti-human TNFα antibodies in combination with ibuprofen in view of the teachings of Ogilvie et al and Smith et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to apply the method of claims 1-7, 36-39 and 69 of U.S. Patent No. 6,509,015 B1 comprising administering the human anti-human TNFα antibodies for the treatment of psoriatic arthritis and optionally administer the human anti-human TNFα antibodies in combination with ibuprofen in view of the teachings of Ogilvie et al and Smith et al because Ogilvie et al teach a method of treating psoriatic arthritis in patients comprising administering the anti-TNFα monoclonal antibody, Infliximab, which resulted in a dramatic improvement in arthritis and showed rapid improvement of their psoriatic arthritis and Smith et al teach that administration of ibuprofen in psoriatic arthritis patients effectively decreases pain and joint swelling. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a method for treating psoriatic arthritis in a subject comprising administering the human anti-human TNFα antibodies of claims 1-7, 36-39 and 69 of U.S. Patent No. 6,509,015 B1 and optionally administer the human anti-human TNFα antibodies in combination with ibuprofen (i.e., at least one additional therapeutic agent), which decreases pain and joint swelling in psoriatic arthritis patients in view of Ogilvie et al and Smith et al.

Claims 1-4, 6, 12, 14-15, 18, 20 and 22-23 are directed to an invention not patentably distinct from claim 1-7, 36-39 and 69 of commonly assigned U.S. Patent No. 6,509,015 B1. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent No. 6,509,015 B1, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions

were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

22. Claims 1-4, 6, 12, 14-15, 18, 20 and 22-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-8 and 10-14 of copending Application No. 11/435,844 in view of Ogilvie et al (British Journal of Dermatology, 144(3):587-589, March 2001) and Smith et al (Arthritis Rheum. 23(8):961-962, August 1980). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims have been described supra.

Claims 1, 4-8 and 10-14 of copending Application No. 11/435,844 are drawn to a method for treating a human subject suffering from erosive polyarthritis comprising administering to the subject a TNFα antibody or antigen-binding fragment thereof such that erosive polyarthritis is treated, wherein the antibody or antigen-binding fragment thereof is human, dissociates from human TNFα with a K_d of 1×10^{-8} M or less and has a K_{off} of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1×10^{-7} M or less, and the human antibody or antigen-binding fragment thereof antibody has the following characteristics: (a) dissociates from human TNFα with a K_{off} of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance; (b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:3, or modified from SEQ ID NO:3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9; (c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:4, or

modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12, and wherein the human antibody or antigen-binding fragment thereof comprises a light chain variable region comprising SEQ ID NO:1 and a heavy chain variable region comprising SEQ ID NO:2, all properties of the human anti-human TNFα antibodies and antigen-binding fragments thereof of the present claims and wherein the TNFα antibody or antigen-binding fragment thereof is administered with a therapeutic agent. Further, the subject has a disorder in which TNFα activity is detrimental and is selected from psoriatic arthritis, ankylosing sopondylitis and juvenile rheumatoid arthritis.

The claims in the instant application are obvious variants of claims 1, 4-8 and 10-14 of copending Application No. 11/435,844 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the method of claims 1, 4-8 and 10-14 of copending Application No. 11/435,844 comprising administering the human anti-human TNFα antibodies for the treatment of psoriatic arthritis and optionally administer the human anti-human TNFα antibodies in combination with ibuprofen in view of the teachings of Ogilvie et al and Smith et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to apply the method of claims 1, 4-8 and 10-14 of copending Application No. 11/435,844 comprising administering the human anti-human TNFα antibodies for the treatment of psoriatic arthritis and optionally administer the human anti-human TNFα antibodies in combination with ibuprofen in view of the teachings of Ogilvie et al and Smith et al because Ogilvie et al teach a method of treating psoriatic arthritis in patients comprising administering the anti-TNFα monoclonal antibody, Infliximab, which resulted in a dramatic improvement in arthritis and showed rapid improvement of their psoriatic arthritis and Smith et al teach that administration of ibuprofen in psoriatic arthritis patients effectively decreases pain and joint swelling. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a method for treating psoriatic arthritis in a subject

comprising administering the human anti-human TNFα antibodies of claims 1, 4-8 and 10-14 of copending Application No. 11/435,844 and optionally administer the human anti-human TNFα antibodies in combination with ibuprofen, which decreases pain and joint swelling in psoriatic arthritis patients in view of Ogilvie et al and Smith et al.

Claims 1-4, 6, 12, 14-15, 18, 20 and 22-23 are directed to an invention not patentably distinct from claim 1, 4-8 and 10-14 of commonly assigned copending Application No. 11/435,844. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned copending Application No. 11/435,844, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

23. Claims 1-4, 6, 12, 14-15, 18, 20 and 22-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23, 73-84 and 86-99 of copending Application No. 10/163,657 in view of Ogilvie et al (British Journal of Dermatology, 144(3):587-589, March 2001) and Salfeld et al [a] (WO 97/29131, publication date 8/14/1997, IDS reference A4 filed 4/6/04) and

Smith et al (Arthritis Rheum. 23(8):961-962, August 1980). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims have been described supra.

Claims 1-23, 73-84 and 86-99 of copending Application No. 10/163,657 are drawn to methods for treating a disorder in which TNFα activity is detrimental comprising administering an anti-TNFα antibody or antigen-binding fragment thereof on a biweekly dosing regimen, wherein the antibody or antigen-binding fragment thereof is a human antibody identical to the human anti-human TNFα antibodies claimed in the instant application, i.e., having identical structures/sequences, binding kinetics and neutralization properties. Claims 1-23, 73-84 and 86-99 of copending Application No. 10/163,657 do not teach the treatment of psoriatic arthritis in a patient comprising administration of the anti-TNFα antibody or antigen-binding fragment thereof in combination with at least one additional therapeutic agent selected from the group consisting of ibuprofen, diclofenac and misoprostol, naproxen, meloxicam, indomethacin and diclofenac. These deficiencies are made up for in the teachings of Ogilvie et al and Salfeld et al [a] and Smith et al.

Ogilvie et al have been described supra.

Salfeld et al [b] have been described supra.

Smith et al have been described supra.

The claims in the instant application are obvious variants of claims 1-23, 73-84 and 86-99 of copending Application No. 10/163,657 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the method of claims 1-23, 73-84 and 86-99 of copending Application No. 10/163,657 comprising administering the human anti-human TNFα antibodies for the treatment of psoriatic arthritis and optionally administer the human anti-human TNFα antibodies in combination with ibuprofen in view of the teachings of Ogilvie et al and Salfeld et al [a] and Smith et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to apply the method of claims 1-

23, 73-84 and 86-99 of copending Application No. 10/163,657 comprising administering the human anti-human TNFα antibodies for the treatment of psoriatic arthritis and optionally administer the human anti-human TNFα antibodies in combination with ibuprofen in view of the teachings of Ogilvie et al and Salfeld et al [a] and Smith et al because Ogilvie et al teach a method of treating psoriatic arthritis in patients comprising administering the anti-TNFα monoclonal antibody, Infliximab, which resulted in a dramatic improvement in arthritis and showed rapid improvement of their psoriatic arthritis and Salfeld et al [a] teach the administration of the human anti-human TNFα antibodies of claims 1-23, 73-84 and 86-99 of copending Application No. 10/163,657, optionally in combination with at least one additional therapeutic agent for inhibiting TNFα activity and Smith et al teach that administration of ibuprofen in psoriatic arthritis patients effectively decreases pain and joint swelling. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a method for treating psoriatic arthritis in a subject comprising administering the human anti-human TNFα antibodies of claims 1-23, 73-84 and 86-99 of copending Application No. 10/163,657 and optionally administer the human anti-human TNFα antibodies in combination with at least ibuprofen as made explicit in the teachings of Salfeld et al [a], i.e., one additional therapeutic agent.

Claims 1-4, 6, 12, 14-15, 18, 20 and 22-23 are directed to an invention not patentably distinct from claims 1-23, 73-84 and 86-99 of commonly assigned copending Application No. 10/163,657. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned copending Application No. 10/163,657, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name

the prior inventor of the conflicting subject matter. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

24. Claims 1-4, 6, 12, 14-15, 18, 20 and 22-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15, 19, 56, 66, 77 and 87 of copending Application No. 11/233,252 in view of Ogilvie et al (British Journal of Dermatology, 144(3):587-589, March 2001) and Salfeld et al [a] (WO 97/29131, publication date 8/14/1997, IDS reference A4 filed 4/6/04) and Smith et al (Arthritis Rheum. 23(8):961-962, August 1980). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims have been described supra.

Claims 15, 19, 56, 66, 77 and 87 of copending Application No. 11/233,252 are drawn to a method for treating a subject suffering from a disorder in which TNFα activity is detrimental comprising administering a pharmaceutical composition comprising an isolated human anti-human TNFα antibody or antigen-binding fragment thereof that dissociates from human TNFα with a K_d of 1×10^{-8} M or less and has a K_{off} of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1×10^{-7} M or less and wherein the pharmaceutical composition is administered with at least one additional therapeutic agent. Claims 15, 19, 56, 66, 77 and 87 of copending Application No. 11/233,252 do not specifically teach human anti-human TNFα antibodies or antigen-binding fragments thereof having a K_{off} of 1×10^{-3} s^{-1} or less and the light and heavy chain CDR3 sequences (SEQ ID Nos:3-4) or variants thereof or comprising the light chain variable region of SEQ ID NO:1 and the heavy chain variable region of SEQ ID

NO:2 or wherein the anti-human TNFα antibody is antibody D2E7 and in combination with ibuprofen. These deficiencies are made up for in the teachings of Ogilvie et al and Salfeld et al [a] and Smith et al.

Ogilvie et al have been described supra.

Salfeld et al [b] have been described supra.

Smith et al have been described supra.

The claims in the instant application are obvious variants of claims 15, 19, 56, 66, 77 and 87 of copending Application No. 11/233,252 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a method for treating psoriatic arthritis in a subject comprising administering the human anti-human TNFα antibodies of Salfeld et al [a], and in combination with ibuprofen in view of the teachings of Ogilvie et al and Smith et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to produce a method for treating psoriatic arthritis in a subject comprising administering the human anti-human TNFα antibodies of Salfeld et al [a], and in combination with ibuprofen in view of claims 15, 19, 56, 66, 77 and 87 of copending Application No. 11/233,252 and of Ogilvie et al and Salfeld et al [a] and Smith et al because Ogilvie et al teach a method of treating psoriatic arthritis in patients comprising administering the anti-TNFα monoclonal antibody, Infliximab, which resulted in a dramatic improvement in arthritis and showed rapid improvement of their psoriatic arthritis and Salfeld et al [a] teach the administration of the human anti-human TNFα antibodies of claims 15, 19, 56, 66, 77 and 87 of copending Application No. 11/233,252, optionally in combination with at least one additional therapeutic agent for inhibiting TNFα activity and Smith et al teach that administration of ibuprofen in psoriatic arthritis patients effectively decreases pain and joint swelling. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a method for treating psoriatic arthritis in a subject comprising administering the human anti-human TNFα antibodies of Salfeld et al [a], and in combination

with ibuprofen in view of claims 15, 19, 56, 66, 77 and 87 of copending Application No. 11/233,252 and Ogilvie et al and Salfeld et al [a] and Smith et al.

Claims 1-4, 6, 12, 14-15, 18, 20 and 22-23 are directed to an invention not patentably distinct from claims 15, 19, 56, 66, 77 and 87 of commonly assigned copending Application No. 11/233,252. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned copending Application No. 11/233,252, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

25. Claims 1-4, 6, 12, 14-15, 18, 20 and 22-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 and 4-14 of copending Application No. 10/622,932; claims 1-11 of copending Application No. 10/623,075; claims 1, 3-14 and 16 of copending Application No. 10/623,318 in view of Ogilvie et al (British Journal of Dermatology, 144(3):587-589, March 2001) and Smith et al (Arthritis Rheum. 23(8):961-962, August 1980). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims have been described supra.

The above cited copending applications claims are drawn to the administration of human anti-human TNFα antibodies and antigen-binding fragments thereof that are identical to the neutralizing, high affinity human anti-human TNFα antibodies and antigen-binding fragments thereof of the present claims, i.e., identical structures/sequences, binding kinetics and neutralization properties, for the treatment of various disorders associated with TNFα activity and wherein the human anti-human TNFα antibodies and antigen-binding fragment thereof are administered with at least one additional therapeutic agent. The above claims of the copending applications do not specifically teach the treatment of psoriatic arthritis and is administered with ibuprofen. These deficiencies are made up for in the teachings of Ogilvie et al and Smith et al.

Ogilvie et al have been described supra.

Smith et al have been described supra.

The claims in the instant application are obvious variants of the above copending applications claims because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a method for treating psoriatic arthritis in a subject comprising administering the human anti-human TNFα antibodies recited the above copending applications, identical to the presently claimed anti-TNFα antibodies and in combination with ibuprofen in view of the teachings of Ogilvie et al and Smith et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to produce a method for treating psoriatic arthritis in a subject comprising administering the human anti-human TNFα antibodies recited the above copending applications, identical to the presently claimed anti-TNFα antibodies and in combination with ibuprofen in view of the teachings of Ogilvie et al and Smith et al because Ogilvie et al teach a method of treating psoriatic arthritis in patients comprising administering the anti-TNFα monoclonal antibody, Infliximab, which resulted in a dramatic improvement in arthritis and showed

rapid improvement of their psoriatic arthritis and Smith et al teach that administration of ibuprofen in psoriatic arthritis patients effectively decreases pain and joint swelling. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a method for treating psoriatic arthritis in a subject comprising administering the human anti-human TNFα antibodies recited in the above copending applications and in combination with ibuprofen in view of Ogilvie et al and Smith et al.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

26. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643